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13. ABSTRACT (Maximum 200 words)

The overall goal of the proposed studies was to further elucidate the mechanisms by which the brainstem noradrenergic (NA) nucleus, locus coeruleus (LC), is capable of altering forebrain electrophysiological activity.

The proposed studies had the following Specific Aims: 1) To examine the relationship between the intensity of LC neuronal activity, forwbrain EEG activation, and rates of NA release in neocortex and hippocampus using microdialysis; 2) To test the hypothesis that LC-induced activation of forebrain EEG is mediated by LC/NA actions on septal and basal forebrain neurons; 3) To examine, in unanesthetized monkey, the effects of activating or inactivating the LA/NA system on forebrain EEG and on dialysis measures of NA and acetylcholine release in neocortex and hippocampus. The effects on these dialysis measures of systemic adrenergic drugs that alter cognitive performance was to be determined; 4) To examine, in monkey, the effects of activating or inactivating the LC/NA system on cortical and hippocampal EEG measures and on complex, bimanual motor behavior.

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FINAL TECHNICAL REPORT
(01 Jul 93 - 30 Jun 96)

CONTRACT: AFOSR-F49620-93-1-0402 (Foote/Haddad/Berry)

TITLE: Extrathalamic Modulation of Cortical Responsiveness

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Objectives: There were no substantial changes in the objectives of this effort which remained those proposed as Specific Aims in the application of December, 1992.

Status of effort: During the three-year funding period for this effort, substantial progress was made in several areas. This final technical report is divided into four sections that correspond to the Specific Aims for Years 07-09 of our project. The 10 full-length reports that were either accepted for publication or actually published during the funding period are listed in the Publications section below. Nearly all of the completed work is summarized and discussed in these publications, and the numbers in square brackets within the text of the report refer to the corresponding publications from this list.

AIM 1: TO EXAMINE THE RELATIONSHIPS AMONG LOCUS COERULEUS (LC) NEURONAL ACTIVITY, FOREBRAIN ELECTROENCEPHALOGRAPHIC (EEG) MEASURES, AND RATES OF NORADRENALINE (NA) RELEASE IN NEOCORTEX AND HIPPOCAMPUS BY PERFORMING MICRODIALYSIS AND OBTAINING EEG MEASURES IN THESE FOREBRAIN REGIONS IN ANESTHETIZED RAT DURING MANIPULATION OF LC ACTIVITY. [Publications 1 and 4]

Effects of LC inactivation on neocortical and hippocampal EEG activity [Publication 1]. Intrabrainstem administration of α_2-agonists into the region of the LC has been observed by others to increase behavioral and EEG measures of sedation. Because these drugs act to inhibit LC neuronal discharge activity and NA release, these observations are consistent with an action of the LC/NA system in the maintenance of an activated forebrain. However, interpretation of results obtained utilizing intratissue drug infusions for the study of LC function is complicated by a variety of factors, such as the small size of the nucleus and the close proximity of the LC to other nuclei known to affect behavioral and EEG states. These factors, together with the absence of electrophysiological measures documenting the relationship between changes in LC neuronal activity and EEG state following such infusions preclude specific conclusions regarding the site(s) of action for the sedative effects of intrabrainstem administered α_2-agonists.

If, in fact, intrabrainstem administered α_2-agonists enhance EEG measures of sedation through an inhibition of LC neuronal discharge activity, it would be hypothesized that: 1) infusions that are effective in suppressing LC activity will alter forebrain EEG; 2) changes in LC neuronal discharge activity will precede changes in forebrain EEG activity; 3) the return of EEG activity to the pre-infusion state will follow the recovery of LC neuronal activity; 4) infusions that are not effective at suppressing LC neuronal discharge activity will not alter forebrain EEG measures.

In these studies, clonidine infusions (35 nl or 150 nl) were made immediately adjacent or approximately 1000 um distant to LC. These infusions were made under conditions in which high-frequency, low-voltage activity predominated in neocortical EEG and theta-activity predominated in hippocampal EEG. The following was observed: 1) cortical and hippocampal activity were not substantially affected following unilateral clonidine-induced LC inactivation; 2) bilateral clonidine infusions that completely suppressed LC neuronal discharge activity in both hemispheres induced a shift in cortical activity to low-frequency, large amplitude activity and the replacement of theta-activity with

mixed frequency activity in hippocampus; 3) 35 nl infusions placed 800-1200 um from the LC did not induce a complete suppression of LC activity and did not alter forebrain EEG; 4) 150 nl infusions placed 800-1200 um from LC were either ineffective at completely suppressing LC neuronal discharge activity or did so with a longer latency to complete LC inhibition and a shorter duration of inhibition; 5) in all cases, the latencies of EEG responses were coincident with the complete bilateral inhibition of LC discharge activity and persisted throughout the period during which bilateral LC neuronal discharge activity was completely absent (60-240 min); 6) the resumption of pre-infusion EEG activity patterns closely followed the recovery of LC neuronal activity or could be induced with systemic administration of the α_2-NA antagonist, idazoxan. These results suggest that the clonidine-induced changes in EEG were dependent on the complete bilateral suppression of LC discharge activity and that, under the present experimental conditions, the LC/NA system exerts a potent and tonic activating influence on forebrain EEG state such that activity within this system is necessary for the maintenance of an activated forebrain EEG state.

LC manipulations and simultaneous cortical microdialysis. We have nearly completed experiments involving cortical microdialysis and peri-LC bethanechol or clonidine infusions to increase or decrease LC neuronal discharge levels in halothane-anesthetized rats. NA was assayed using HPLC with electrochemical detection. In 25 cases, rats were implanted with dialysis probes 2-3 hours prior to initiation of baseline sample collection. This procedure yielded stable baseline NA levels throughout the experiment which was conducted over the next few hours. In 20 additional cases, rats were implanted with dialysis probes the day prior to the experimental session. This was done because there is evidence that during the first 3-8 hours following dialysis probe insertion, a significant fraction of NA release is impulse independent. In the latter cases, rats were anesthetized with halothane, the dialysis probes implanted, and the rats replaced in their home cages. The following day, the rats were anesthetized with halothane, the LC located, and the experiment conducted exactly as the other 12. In all cases, 2-3 hours following initiation of halothane anesthesia, 3-4 20-min baseline samples were collected. At this point, a bethanechol or clonidine infusion (1-8 ng/nl) was made at the start of a dialysis sampling interval. At the end of this 20-min sample, a recovery sample was collected, followed by a sample during which the LC was again manipulated, followed by 1-2 recovery samples. Infusions that increased LC neuronal discharge levels to a maximum of approximately 3 times basal levels, with a total duration of activation of approximately 10 min, resulted in a 50-100% increase in NA in dialysate samples. NA concentrations returned to baseline levels in the sample immediately following LC activation, and comparable NA responses were consistently observed with repeated LC activation. Bethanechol infusions that increased LC neuronal discharge levels to a maximum of approximately 5-6 times basal levels, with a total duration of activation of approximately 15-20 min, also increased NA concentrations 50-100%. Thus, there appears to be a ceiling beyond which increased LC discharge does not result in a corresponding increase in NA release. However, up to this point there is a generally linear increase in NA release that is proportional to the magnitude of increase in LC discharge activity. When clonidine infusions are used to reduce LC activity, there is also generally a proportional decrease in frontal cortex NE release. The major exception to this relationship is that LC activity can be reduced to 5 - 10% of baseline levels, while extracellular NE remains at 25 - 30% of its resting levels. This could result from input from the contralateral LC or it could result from residual

ipsilateral LC activity that is not being detected by our recording electrode. However, it could actually be an indication that there is a low level of impulse-independent NE release. **[These data were presented at the 1996 Society for Neuroscience meeting; Berridge, C.W., Abercrombie, E.A., Kuczenski, R.T., and Foote, S.L. Relationships between locus coeruleus neuronal activity and norepinephrine release in neocortex.]**

AIM 2: TO TEST THE HYPOTHESIS THAT LC-INDUCED ACTIVATION OF FOREBRAIN EEG IS MEDIATED BY LC/NA ACTIONS ON CHOLINERGIC AND/OR NON-CHOLINERGIC NEURONS WITHIN BASAL FOREBRAIN NUCLEI. [Publications 8 and 9]

Involvement of the medial septal region in LC/NA modulation of forebrain EEG. The basal forebrain cholinergic nuclei, located in the substantia innominata/nucleus basalis of Meynert and the medial septal area/diagonal band of Broca are thought to play important roles in the modulation of cortical and hippocampal EEG. These nuclei receive a dense LC/NA innervation. We have initiated a series of experiments designed to determine whether LC/NA influences on forebrain EEG state are mediated by these nuclei. Initially, the effects of the β-agonist, isoproterenol (ISO), and the β-antagonist, timolol (TIM), infused into the medial septum on cortical and hippocampal EEG were examined in halothane-anesthetized rats. In order to perform a preliminary evaluation of this hypothesis, the following 3 questions were examined in approximately 60 rats: 1) What is the effect of ISO when infused into the medial septum under conditions in which slow-wave activity predominates in neocortex and hippocampus? 2) What is the effect of ISO infused outside the region of medial septum? 3) What is the effect of TIM infused bilaterally into the medial septum under conditions in which cortical and hippocampal EEG are activated? 4) What is the effect of TIM infused bilaterally into medial septum on peri-LC bethanechol-induced EEG activation? In these experiments, 26 ga. guide cannulae were implanted over left and right medial septum, penetrating cortex 1.5 mm at an angle of 4° to permit placement of a 33 ga. infusion needle into medial septum while avoiding damage to the superior sagittal sinus and fibers of passage that travel along the most medial aspect of the septal area. Infusions consisted of 100-150 nl of vehicle or drug, at a concentration of 25 ug/ul, infused over a 1-min period. Halothane was adjusted to permit the appropriate level of anesthesia, dummy infusion needles were placed into left and right cannulae and 30-45 min of baseline EEG was collected. 10 min prior to a medial septum infusion, the dummy needle was removed and a needle loaded with 2% Pontamine Sky Blue dye in phosphate buffer saline or drug dissolved in this solution was inserted.

Bilateral vehicle infusions into the medial septum had no obvious EEG effects. In contrast, 1-10 min following 100-150 nl of unilateral ISO, hippocampal theta activity was substantially increased bilaterally and, in the majority of cases, there was a less robust but clear decrease in cortical slow-wave activity. The duration of these responses ranged from 20 min to greater than 60 min and could be reversed with TIM infusion. Identical volumes of ISO infused into the striatum a similar distance from the lateral ventricle had no EEG effects, indicating that these effects of ISO are not due to diffusion into the ventricular system and action at a distant site. Similarly, ISO had no effects on forebrain EEG when infused into the lateral septum or directly into the lateral ventricle approximately 1 mm posterior to the posterior end of medial septum, or into substantia innominata.

Under conditions in which forebrain EEG was in an activated state, unilateral TIM infusion had no EEG effects. In contrast, bilateral TIM resulted in a shift in hippocampal EEG from nearly pure-theta activity to mixed frequency activity and the appearance of large-amplitude, slow-wave activity in cortex.

The effects of TIM on peri-LC bethanechol-induced EEG activation were also examined. In these experiments, peri-LC infusions were made under 3 experimental conditions; prior to any septal infusions, 10 min following bilateral medial septal vehicle infusions, or 10 min following bilateral medial septal TIM infusions. Bilateral TIM blocked or severely attenuated the peri-LC bethanechol-induced activation of cortical and hippocampal EEG.

To summarize, as was observed with unilateral LC activation, unilateral infusions of the β-agonist, ISO, elicited bilateral EEG activation in hippocampus and cortex. Unilateral medial septal infusions of the β-antagonist, TIM, had no effect on either cortical or hippocampal EEG, whereas bilaterally infused TIM substantially decreased indices of EEG activation in both structures.

One possible explanation for the lack of effects of ISO when infused into substantia innominata on either cortical or hippocampal EEG is that, given the relatively large size of this area and the relatively small infusion volumes, the drug was not diffusing throughout an adequate volume of the structure to elicit EEG changes. Therefore, in an additional 4 cases, unilateral and bilateral ISO infusions were made in which the concentration of the drug was doubled and the infusion volume was either doubled (300 nl) or tripled (450 nl). These infusions had no obvious consistent effects on either hippocampal or cortical EEG.

We have also evaluated the effects of small infusions of ISO into MS in unanesthetized rats to determine whether they alter behavioral, EEG, and electromyographic (EMG) measures of sleep and waking in the resting, undisturbed state. These infusions resulted in a significant increase in time spent awake, defined by both behavioral and EEG/EMG measures, and in the nearly complete suppression of REM sleep. EEG/EMG responses either coincided with or preceded behavioral responses by 10-320 seconds. The pattern of behavioral responses observed following MS-ISO infusions was qualitatively similar to that associated with normal waking. Infusions of vehicle into MS or ISO into sites adjacent to MS did not elicit consistent alterations in behavioral state. These results suggest that the LC noradrenergic system exerts potent behavioral and EEG-activating effects via actions of NE at beta-receptors located within MS.

AIM 3: TO EXAMINE, IN MONKEY, THE EFFECTS OF ACTIVATING OR INACTIVATING THE LC/NA SYSTEM ON EEG AND ON DIALYSIS MEASURES OF THE RELEASE OF NA AND OTHER MONOAMINES IN NEOCORTEX AND HIPPOCAMPUS. THE EFFECTS ON THESE EEG AND DIALYSIS MEASURES OF SYSTEMICALLY ADMINISTERED ADRENERGIC DRUGS THAT ALTER COGNITIVE PERFORMANCE WILL ALSO BE DETERMINED. [Publications 5 and 6]

The effects of systemically administered adrenergic agents on monkey P300s [Publication 6]. In previous funding periods we have characterized and studied the neural substrates of a monkey event-related potential component that exhibits many of the characteristics of the P3 or P300 components of human event-related potentials. The study to be summarized in this section evaluated the role of NA in the modulation of an auditory version of this P300 response.

In this study, EEG, behavioral, and event-related potential data were collected from squirrel monkeys in an auditory "oddball" paradigm in which the subjects could bar-press for a food reward only during a short interval following the occurrence of target stimuli that were embedded within repetitively occurring non-target stimuli. Data were obtained following the systemic administration of placebo or clonidine, an α_2-noradrenergic agonist that suppresses LC activity and NA release. Clonidine significantly decreased the area and increased the latency of the P300-like potential that occurred following target stimuli, while leaving earlier peaks unaffected. Rates of behavioral responding were not diminished following clonidine administration. This indicates that the suppression of the P300-like potential was not due to sedation.

LC neuronal activity in awake monkeys: relationship to spontaneous EEG and auditory P300-like potentials [Publication 5]. These experiments were designed to test the hypothesis that novel auditory stimuli lead to phasic and/or tonic increases in LC discharge activity, which may be a necessary condition for the occurrence of P300 potentials. Event-related potentials and LC unit activity were recorded simultaneously in 3 untrained macaque (Macaca fascicularis) monkeys during the presentation of an auditory oddball paradigm. Oddball stimuli resulted in probability-sensitive, P300-like potentials. While these event-related potential findings are novel, we were able to obtain only a limited number of high-quality LC recordings in this paradigm. Three of 12 LC units showed small phasic enhancements of LC firing after infrequent but not frequent tones. In an additional set of studies, one monkey was trained to bar-press in response to the occurrence of the target stimulus in the oddball paradigm. Interestingly, this animal displayed a prominent P300-like wave, but only when he performed the oddball task accurately. In sessions where the monkey did not respond, neither P300-like potentials nor phasic LC responses were elicited by target stimuli. However, LC cells did tend under these conditions to show a tonic elevation in firing following targets. For the 2 LC neurons whose activity we were able to record during sustained, accurate performance of the task, phasic discharge activity was observed following the presentation of targets, and the timing of this activity indicated it was related to the behavioral response rather than to stimulus presentation. Finally, comparisons of the discharge activity of individual LC neurons with EEG recordings, under circumstances where no stimuli were presented to these subjects, confirmed our previous observations in squirrel monkey that LC discharge activity is strictly correlated with, and anticipates by 500 to 1000 msec, changes in cortical EEG.

Assessment of monoamine release via microdialysis in unanesthetized monkey. We have now developed successful microdialysis methods for assessing extracellular monoamine concentrations in awake, chair-restrained cynomolgus monkeys (Macaca fascicularis). This involved the development of techniques and equipment, as well as implementing procedures. Amphetamine administration was used in the early feasibility experiments to evaluate the appropriateness of the procedures. The effects of locally infused and/or systemically administered amphetamine, potassium, fenfluramine, and fluoxetine have now been assessed in several experiments each in order to demonstrate the specificity and sensitivity of these methods. We have now completed a study in which we used these methods to determine the effects of acute and chronic fluoxetine administration on extracellular levels of serotonin (5-HT) and dopamine (DA).

Because monkeys exhibit large individual differences in brain structure and

size, and thus stereotaxic coordinates, for both cortical and subcortical structures, the initial step for this study was to perform an MRI brain scan on each animal to accurately determine the stereotaxic locations of target structures. With the head fixed in a plastic stereotaxic instrument, MRI scans were performed in the 3 standard stereotaxic planes. The resulting images were subjected to a detailed analysis in order to determine the stereotaxic locations of target structures.

After a two-week recovery period, each monkey underwent surgery for the implantation of dialysis guide cannulae and a device for later immobilizing the head. Using aseptic techniques, guide cannulae were cemented in place bilaterally over several brain regions, e.g., the caudate, cingulate cortex, and primary motor cortex. The device that was later used to immobilize the head during chairing also served to hold a protective cap to prevent access by the animal to the cannulae and other parts of the head implant while he was in his home cage. After recovery from surgery, the monkey was habituated to the chairing procedure in daily sessions, including having the head fixed in position for 2-3 hours at a time. Following an additional 1-month period, collection of dialysis samples was initiated. 4-6 dialysis probes were inserted per session, and each session consisted of 2 days of dialysis. On Day 1, the animal was chaired, the head fixed, dialysis probes inserted, the cap replaced, and the animal returned to its home cage. On Day 2, the animal was chaired, the head fixed, probes were connected to the perfusion pump, and sample collection was conducted. Sessions were separated from each other by a 1-2 week period. After 5 such sessions, all possible sites had been used. At this time, the animal was deeply anesthetized, dye was infused through dialysis probes reinserted through each of the guide cannulae, and the animal was perfused using our standard protocol for immunohistochemical experiments.

The results of our attempts to dialyze a single site over several days, or to reinsert dialysis probes into previously used sites, indicated that such an approach is not currently feasible. In both cases, basal dialysate DA, NA, and their metabolites were substantially decreased, in some cases below detection limits, and the responses to amphetamine challenge were significantly diminished, and in some cases no longer evident. We and others have observed similar changes following repeated probe insertions into rodent brain. For these reasons, we now use each dialysis site only once. Histological analyses revealed that the MRI procedure substantially enhanced the accuracy of guide-cannula placement, relative to a purely stereotaxic approach. Most of the probe sites were found to be within 0.5 mm of their intended locations.

In summary, it has been possible to reliably detect and quantify stable baseline levels for all 3 monoamine transmitters (norepinephrine, serotonin, and dopamine). It has also been possible to demonstrate that each of these transmitters shows appropriate changes in extracellular levels following local or systemic administration of drugs known to enhance or reduce such levels in rodent brain. Furthermore, we have accurately placed probes in a number of structures and found interesting regional differences in the baseline levels and pharmacological responses of specific transmitters. Thus, these results demonstrate the feasibility of applying microdialysis methodologies, and of measuring extracellular DA, NA, and 5-HT, as well as their catabolites in cortical and subcortical regions in awake monkey. Our microdialysis studies of the effects of fluoxetine were presented at the 1996 meeting of the Society for

Neuroscience; **Smith, T.D., Kuczenski, R., and Foote, S.L. Monoaminergic dynamics during chronic fluoxetine administration: in vivo microdialysis in awake monkeys.**

AIM 4: TO EXAMINE, IN MONKEY, THE EFFECTS OF ACTIVATING OR INACTIVATING THE LC/NA SYSTEM ON NEOCORTICAL AND HIPPOCAMPAL EEG MEASURES AND ON COORDINATED BIMANUAL MOTOR BEHAVIOR.

We only completed experiments on the first monkey to be used in these studies, and results were mixed. It appears that clonidine infusions were successfully made into the LC region, but our LC recordings were not of sufficient quality and/or reliability to allow us to determine whether these infusions were effective in altering LC discharge activity. However, we are encouraged that we have hardware that appears capable of directing the placement of the LC recording microelectrode and the infusion needle in the appropriate brain region. Also, we have hopefully collected some "control" data demonstrating that infusions into surrounding brainstem regions are ineffective in producing large changes in behavior or EEG.

OTHER ACTIVITIES

The results obtained during the past few years in this project have also appeared in some of the review articles and book chapters the PI has published during this support period **[Publications 2,7, and 10]**.

Personnel Supported:

Stephen L. Foote, Ph.D., PI: Professor of Psychiatry, UCSD
Craig W. Berridge, Ph.D.: Postdoctoral Fellow, now Assistant Professor of Psychology, University of Wisconsin
Raul Harris-Collazo, Ph.D.: Postdoctoral Fellow

Publications:

1. Berridge, C.W., Page, M.E., Valentino, R.J., and Foote, S.L. Effects of locus coeruleus inactivation on electroencephalographic activity in neocortex and hippocampus. Neuroscience 55: 381-393, 1993.

2. Berridge, C.W., Arnsten, A.F.T., and Foote, S.L. Noradrenergic modulation of cognitive function: clinical implications of anatomical, electrophysiological, and behavioral studies in animal models (Editorial). Psychol. Med. 23: 557-564, 1993.

3. Page, M.E., Berridge, C.W., Foote, S.L., and Valentino, R.J. Corticotropin-releasing factor in the locus coeruleus mediates EEG activation associated with hypotensive stress. Neurosci. Lett. 164:81-84, 1993.

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5. Swick, D., Pineda, J.A., Schacher, S., and Foote, S.L. Locus coeruleus neuronal activity in awake monkeys: relationship to auditory P300-like potentials and spontaneous EEG. Exp. Brain Res., 101: 86-92, 1994.

6. Swick, D., Pineda, J.A., and Foote, S.L. Effects of systemic clonidine on auditory event-related potentials in squirrel monkeys. Brain Res. Bull. 33: 79-86, 1994.

7. Foote, S.L. and Aston-Jones, G. Pharmacology and physiology of central noradrenergic systems. Psychopharmacology: The Fourth Generation of Progress. Bloom, F.E. and Kupfer, D.J. (Eds.), Raven Press, New York. pp. 335-345, 1995.

8. Berridge, C.W. and Foote, S.L. Enhancement of behavioral and electroencephalographic indices of waking following stimulation of noradrenergic beta-receptors within the medial septal region of the basal forebrain. J. Neurosci. 16: 6999-7009, 1996.

9. Berridge, C.W., Bolen, S.J., Manley, M.S., and Foote, S.L. Modulation of forebrain electroencephalographic activity in halothane-anesthetized rat via actions of noradrenergic beta-receptors within the medial septal region. J. Neurosci. 16: 7010-7020, 1996.

10. Foote, S.L. The primate locus coeruleus: the chemical neuroanatomy of the nucleus, its efferent projections, and its target receptors. In: Handbook of Chemical Neuroanatomy. Bloom, F.E. (Ed.), Elsevier Science, Amsterdam. In press.

Interactions/Transitions

a. Participation/presentations at meetings: Presentations at CINP (Collegium Internationale Neuro-Psychopharmacologicum) XIXth Congress for Decade of the Brain, Washington, D.C.; Society for Neuroscience Annual Meeting, Miami, Florida; First World Congress on Stress, Bethesda, Maryland; Research Institute of the Scripps Clinic, La Jolla, California; International Catecholamine Symposium.

b. Consultative and advisory functions: Completed 4 years of service on NIH Neurology B (2) Initial Review Group. Chair, NIMH Special Review Study Section.

c. Transitions: None

New discoveries, inventions, or patent disclosures.

None

Honors/Awards.

Stephen L. Foote: Member, Governing Board, McDonnell-Pew Center for Cognitive Neuroscience, San Diego.